

## Claims

1. Microcapsules for use in a pharmaceutical formulation comprising microparticles of amoxicillin coated with at least one coating film comprising:

- 5 (a) at least one film-forming polymer (PI) present in a quantity of 50 to 90% by weight of dry matter of the whole coating composition, and comprising at least one water insoluble cellulose derivative;
- (b) at least one nitrogen-containing polymer (P2), present in a quantity of 2 to 25% by weight of dry matter of the whole coating composition, and consisting of at least one polyacrylamide
- 10 and/or one poly-N-vinylamide and/or one poly-N-vinyl-lactam;
- (c) at least one plasticiser present in a quantity of 2 to 25% by weight of dry matter of the whole coating composition, selected from the group consisting of glycerol esters, phthalates, citrates, sebacates, cetylalcohol esters, castor oil and cutin; and
- (d) optionally at least one surface-active and/or lubricating agent, present in a quantity of 2 to
- 15 20% by weight of dry matter of the whole coating composition, and selected from one or more of anionic surfactants, and/or from nonionic surfactants, and/or from lubricants selected from stearates, stearyl fumarates, lauryl sulfate and/or glyceryl behenate;
- said microparticles of amoxicillin having a particle size of between 50 and 1000  $\mu\text{m}$ ; and
- said coating being present in from 5 to 45 % by weight of the granule.

20 2. Microcapsules as claimed in claim 1 in which the film-forming polymer (PI) is present in a quantity of 50 to 80%, more preferably 60 to 80%, by weight of dry matter of the whole coating composition.

25 3. Microcapsules as claimed in claim 1 in which the film-forming polymer (PI) is ethyl cellulose.

4. Microcapsules as claimed in claim 3 in which the ethyl cellulose is used as an aqueous dispersion in water.

30 5. Microcapsules as claimed in claim 1 in which the nitrogen-containing polymer (P2) is present in a quantity of 2 to 20%, more preferably 10 to 20%, by weight of dry matter of the whole coating composition.

6. Microcapsules as claimed in claim 1 in which the nitrogen-containing polymer (P2) is polyvinylpyrrolidone.

7. Microcapsules as claimed in claim 1 in which the plasticiser is present in a quantity of 4 to 15%, more preferably 5 to 10% by weight of dry matter of the whole coating composition.

8. Microcapsules as claimed in claim 1 in which the plasticiser is: dibutyl sebacate, triethyl citrate or castor oil, more preferably castor oil, for use with ethyl cellulose in an organic or aqueous alcohol solvent system solvent; or, a citrate such as triethyl citrate or a sebacate such as dibutyl sebacate, for use with an aqueous dispersion of ethylcellulose.

9. Microcapsules as claimed in claim 1 in which the surface-active and/or lubricating agent is preferably present in a quantity of 2 to 15%, more preferably 2 to 10%, still more preferably 2 to 8%, by weight of dry matter of the whole coating composition.

10. Microcapsules as claimed in claim 1 in which the coating composition comprises ethylcellulose present in from 60 to 80%, polyvinylpyrrolidone present in from 10 to 20%, castor oil present in from 5 to 10%, and polyoxyl 40 hydrogenated castor oil present in from 2 to 8%, by weight of the of dry matter of the whole coating composition.

11. Microcapsules as claimed in claim 10 in which the coating composition comprises ethyl cellulose (about 70 to 72%), polyvinylpyrrolidone (about 16 to 18%), castor oil (about 8%) and polyoxyl 40 hydrogenated castor oil (about 4%),  $\pm 5\%$  of each component, by weight of the of dry matter of the whole coating composition.

12. Microcapsules as claimed in claim 1 in which the coating composition is prepared from an aqueous dispersion of ethyl cellulose and comprises ethyl cellulose present in from 60 to 80%, cetyl alcohol present in from 4 to 10%, sodium lauryl sulfate present in from 2 to 5%, polyvinylpyrrolidone present in from 2 to 10%, and dibutyl sebacate present in from 10 to 25 %, respectively, by weight of the of dry matter of the whole coating composition.

13. Microcapsules as claimed in claim 12 in which the coating composition comprises ethyl cellulose (about 70 to 72%), polyvinylpyrrolidone (about 16 to 18%), castor oil (about 8%) and polyoxyl 40 hydrogenated castor oil (about 4%),  $\pm 5\%$  of each component, by weight of the of dry matter of the whole coating composition.

14. Microcapsules as claimed in claim 12 in which the coating composition prepared is from an aqueous dispersion of ethyl cellulose and comprises ethyl cellulose (about 84 %), polyvinylpyrrolidone (about 3 %), and dibutyl sebacate or triethyl citrate (about 13 %), respectively,  $\pm 5\%$  of each component, by weight of the three components.
15. Microcapsules as claimed in claim 1 in which the coating represents from 5 to 45%, more preferably from 7 to 20%, advantageously from 10 to 15 %, of the weight of the microcapsules.
16. Microcapsules as claimed in claim 1 in which have a second coating layer which is an enteric coating.
17. Microcapsules as claimed in claim 1 in which the particle size of the amoxicillin microparticles is between 100 and 750  $\mu\text{m}$ , more preferably, between 100 and 500  $\mu\text{m}$ , advantageously between 200 and 400  $\mu\text{m}$ , more advantageously between 250 and 400  $\mu\text{m}$ .
18. Microcapsules as claimed in claim 1 which comprise amoxicillin in an amount of between 55 and 95 %, more preferably between 75 and 95 %, advantageously between 85 and 95 %, by weight of the microcapsule.
19. Microcapsules as claimed in claim 1 which release between 10 and 30 % amoxicillin after 0.5 h, between 40 and 60 % after 2 h and at least 70 % after 6 h (measured at pH 6.8).
20. A process for preparing microcapsules of amoxicillin as defined in any one of the preceding claims which process comprises applying in a film coating apparatus a coating composition prepared by admixing the components of the film coating in a solvent system to microparticles of amoxicillin and thereafter drying the microcapsules thus obtained, and optionally, and if necessary, admixing these microcapsules with at least one anti-agglomerating agent.
21. A process as for preparing microcapsules as claimed in claim 20 in which the solvent is an aqueous alcohol.
22. A process as for preparing microcapsules as claimed in claim 20 in which the solvent is water.

23. Microcapsules as claimed in claim 1 obtainable by applying a coating composition prepared by admixing the components of the film coating in an aqueous solvent system to microparticles of amoxicillin and thereafter drying the microcapsules thus obtained.

5 24. A modified release pharmaceutical formulation which comprises amoxicillin, and optionally potassium clavulanate such that the ratio of amoxicillin to clavulanate (if present) is from 2:1 to 30:1, and in which from 30 to 100% of the amoxicillin content is present as microcapsules of amoxicillin, as defined in any of claims 1 to 21 or 25, to provide a slow release phase and from 0 to 70% of the amoxicillin content is present in an immediate release form, to provide an  
10 immediate release phase, further admixed with pharmaceutically acceptable excipients.

25. A modified release pharmaceutical formulation as claimed in claim 24 in which the ratio of amoxicillin to clavulanate is from 2:1 to 20:1, more preferably 6:1 to 20:1, more preferably 12:1 to 20:1, most preferably 14:1 to 16:1.

15 26. A modified release pharmaceutical formulation as claimed in claim 24 in which from 40 to 100%, more preferably from 50 to 90%, of the amoxicillin content is present as microcapsules of amoxicillin.

20 27. A modified release pharmaceutical formulation as claimed in claim 26 in which the Area Under the Curve (AUC) value is substantially similar to, for instance at least 80%, preferably at least 90%, of that of the corresponding dosage of amoxicillin taken as a conventional (immediate release) formulation, over the same dosage period.

25 28. A modified release pharmaceutical formulation as claimed in claim 24 which is provided as a single dose sachet.

29. A modified release pharmaceutical formulation as claimed in claim 28 which comprises from 250 to 3000 mg of amoxicillin, for instance 250, 500, 600, 800, 1000, 1500, 2000, 2500,  
30 3000 mg amoxicillin.

30. A modified release pharmaceutical formulation as claimed in claim 28 which comprises from 2000 mg amoxicillin and 125 mg of clavulanate.

31. A modified release pharmaceutical formulation as claimed in claim 24 which is provided as a dry powder formulations for paediatric use for reconstitution into aqueous suspension.

32. A modified release pharmaceutical formulation as claimed in claim 31 which comprises from 200 to 1200 mg of amoxicillin per unit amount of formulation, and optionally from 25 to 80 mg of clavulanate per unit amount of formulation, such that the ratio of amoxicillin to clavulanate is in the range 2:1 to 30:1.

33. A modified release pharmaceutical formulation as claimed in claim 24 which provides a mean plasma concentration of amoxicillin of 4 µg/mL for at least 4.6 h, preferably at least 4.8 h, more preferably at least 5.5 h, typically between 5.5 and 6.5 h.

34. A modified release pharmaceutical formulation as claimed in claim 24 which provides mean maximum plasma concentration ( $C_{max}$ ) of amoxicillin which is at least 12 µg/mL, preferably at least 14 µg/mL, most preferably at least 16 µg/mL, typically from 16 to 20 µg/mL.

35. A modified release pharmaceutical formulation comprising microcapsules as defined in claim 1 and which is bioequivalent to any one of the formulations hereinbefore exemplified in Examples 10 to 14 and Examples 16 and 17.

36. The use of amoxicillin and optionally clavulanate in the manufacture of a medicament, as defined in claim 24, for treating bacterial infections, in particular in adult patients, at intervals of about 12 h.

37. A method of treating bacterial infection in a paediatric patient which method comprises administering to a patient in need thereof a dosage of from 80 to 180 mg/kg/day of amoxicillin, preferably from 120 to 160, more preferably about 150 mg/kg/day and, optionally, from 6 to 11 mg/kg/day, in divided dosages every 12 h, from a modified release formulation.